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Familial ALS with extreme phenotypic variability due to the I113T SOD1 mutation

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Abstract

We describe a large family with amyotrophic lateral sclerosis (ALS) caused by an I113T mutation in superoxide dismuatse type 1 (SOD1). The proband developed symptoms typical for ALS at age 39 years and is still walking five years later. Marked phenotypic variability is manifested by her mother with onset of gait difficulty and decision-making problems at age 67 years and a five-year course marked by progressive mild upper motor neuron weakness, frontotemporal dementia and chorea. An aunt's initial symptoms included foot numbness and an uncle with the mutation is asymptomatic. Penetrance is only 50% at age 60 years and 88% at age 80 years with an 86-year-old woman harboring the mutation and having a normal neurologic examination. This family highlights the extreme variability in age of onset, clinical manifestations, disease progression and penetrance due to the I113T SOD1 mutation.

Key words: *Superoxide dismutase-1, phenotypic variation, reduced penetrance, frontotemporal dementia, chorea*

Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of upper and lower motor neurons resulting in spasticity, hyper-reflexia, weakness and atrophy. Frontotemporal cognitive impairment is present in up to 50% of patients and dementia may occur in 5% (1). Most patients are sporadic, but about 10% have familial ALS (FALS). The most common mutation is in superoxide dismutase type 1 (SOD1), and has been found in about 20% of families (2,3) and up to 7% of sporadic ALS (3,4).

Over 140 different disease causing mutations have been identified in SOD1, with different mutations causing different phenotypes as related to age of onset, disease duration, penetrance and clinical manifestations. For example, the A4V mutation has high penetrance and uniform rapidly progressive lower motor neuron (LMN) disease resulting in death after an average of 1.5 years (2). In contrast, the I113T mutation causes a late age of onset, incomplete penetrance and variable phenotype (2,3). Clinical features of SALS and FALS are similar, but predominant upper motor neuron (UMN) disease and dementia are rare in FALS, while predominant LMN disease and non-motor symptoms are more common in FALS (5). We examined a large family with FALS and an I113T mutation causing extreme phenotypic variability.

Methods

Patient evaluations

The proband was first examined in our ALS clinic in 2004. In June 2006, after obtaining approval from our institutional review board, we performed complete histories and neurological exanimations on 20 at-risk patients over one day without knowledge of their

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mutation status. Three other symptomatic patients have been examined in our clinic and seven patients sent a saliva specimen for DNA extraction and filled out a history questionnaire, but were not examined. We therefore have DNA and histories on 31 patients and neurologic examinations on 24 patients. Electrophysiological testing was performed on all four patients examined in our clinic and on two of 20 patients examined in June 2006 because of signs and symptoms consistent with ALS.

DNA extraction/PCR

DNA samples were obtained from either white blood cells using the Gentra Puregene kit (Qiagen), or from saliva using the Oragene DNA collection kit (Genotek). Direct sequencing in both the forward and reverse direction was performed after PCR amplification of exon 4 of the SOD1 gene, using standard methods. The sequences of the PCR primers used are available upon request.

Results

Family characteristics

Fifteen of 31 patients were found to have the SOD1 I113T mutation (Table I, Figure 1). Five patients with the mutation had no symptoms, ages 18–69 years, with four having a normal neurologic examination (one patient not examined). Two patients (ages <30 years) were omitted from the table to maintain anonymity. In addition, two other patients (ages 47 and 86 years) had mild symptoms, but did not think they had ALS, and had normal examinations. One complained of unilateral arm pain and the other, an 86-year-old, had gait difficulty secondary to pain, but was walking unassisted.

Eight patients had symptoms consistent with ALS, but with much variability. Age of onset was between 37 and 67 years (mean 53 years), and disease duration was between two and 10 years (mean 5.1 years, excluding one patient who died from sepsis). Two patients had only muscle fasciculations or cramps for five and 10 years. Examination in one of these was normal except for a single brisk deep tendon reflex (DTR) while the other had mild distal weakness and increased DTRs, but normal electromyography (EMG). If all members of our pedigree with a mutation have ALS, then the penetrance is 50% at age 60 years, and 88% at age 80 years.

Variability was most evident in offspring of II 3. III 15 noted distal numbness and weakness as the initial symptom, slowly progressed, and died seven years from symptom onset due to respiratory failure. III 16 had no symptoms and a normal examination, while his child complained of fasciculations, cramps, leg weakness and mild dysarthria. III 13, the mother of the proband (IV 22), is detailed below.

Case reports

IV 22 noted leg cramps and fasciculations at age 39 years. Two months later she could not stand on her right tiptoes. Weakness progressed in the right

Table I. Clinical characteristics of patients with SOD1 mutations.

Patient	Sex	Onset age (years)	Exam age (years)	Initial symptoms	Course	UMN signs	LMN signs	Bulbar signs	Electrodiagnostic studies
IV 22	F	39	44	R. leg weakness	Uses walker, still typing	Yes	Yes	No	C/T/LS Fibs/PSWs normal SNAPs
III 13	F	67	72	Gait difficulty L. arm weakness	Frequent falls cognitive decline chorea/dystonia	Yes	No	Yes	Non-specific No Fibs/PSWs
III 15	F	60	67	Distal numbness and weakness	Respiratory failure; death	Yes	Yes	Yes	C/T/LS Fibs/PSWs absent SNAPs
III 7	F	61	62	L. arm weakness	Sepsis related death (not ALS)	Yes	Yes	No	C/T/LS Fibs/PSWs normal SNAPs
III 18	M	64	66	Fasciculations, cramps, fatigue	Mild weakness	Yes	Yes	No	C/T/LS Fibs/PSWs normal SNAPs
IV 27	F	37	39	Fasciculations, cramps L. leg weakness	Mild dysarthria	ND	ND	ND	ND
III 8	F	44	54	Fasciculations	No weakness	Yes*	Yes*	No	Normal
III 12	F	55	60	Fasciculations, cramps	No weakness	Yes†	No	No	ND
II 5	F	81	86	Gait difficulty due to pain	No weakness	No	No	No	ND
III 21	F	46	47	L. arm pain	No weakness	No	No	No	ND
III 16	M	–	62	None		No	No	No	ND
III 17	F	–	69	None		No	No	No	ND
III 19	M	–	67	None		No	No	No	ND

Abbreviations: C/T/LS: cervical/thoracic/lumbosacral; Fibs/PSWs: fibrillations/positive sharp waves; SNAP: sensory nerve action potential; ND: not done; *mild; †1 brisk DTR.

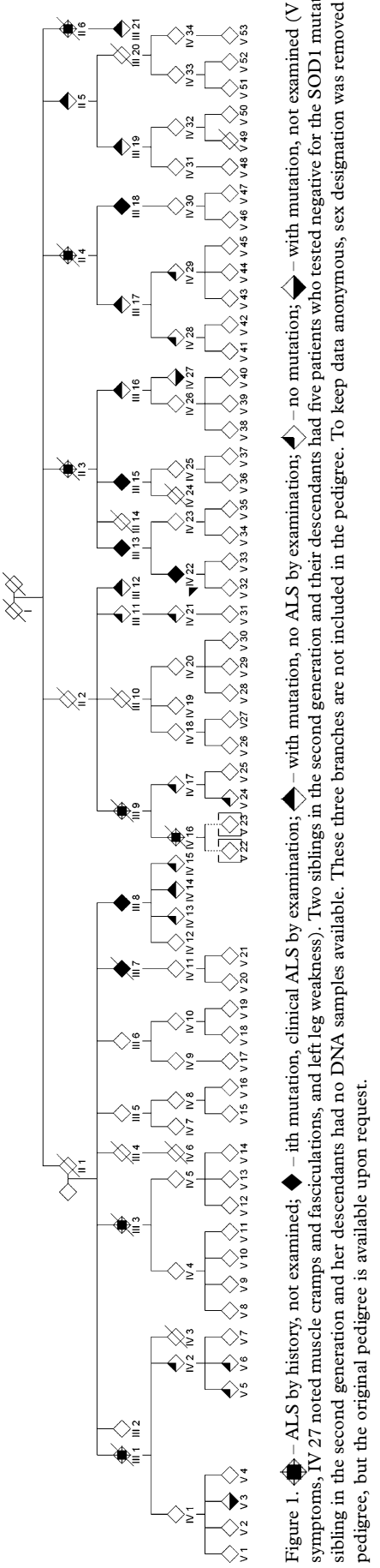

Figure 1. ◆ – ALS by history, not examined; ◆ – ith mutation, clinical ALS by examination; ◆ – with mutation, no ALS by examination; ◇ – no mutation; ◆ – with mutation, not examined (V 3 had no symptoms, IV 27 noted muscle cramps and fasciculations, and left leg weakness). Two siblings in the second generation and their descendants had five patients who tested negative for the SOD1 mutation. One sibling in the second generation and her descendants had no DNA samples available. These three branches are not included in the pedigree. To keep data anonymous, sex designation was removed from the pedigree, but the original pedigree is available upon request.

and began in the distal left leg and she noted arm fasciculations, but denied arm weakness, dysarthria or dysphagia. Neurologic examination showed mild hand muscle weakness, 4/5 ankle dorsiflexor and plantar flexor weakness, worse on the right and brisk DTRs, except absent at the ankles. Electrodiagnostic studies showed small motor responses from the feet, normal sensory responses and EMG evidence of widespread acute denervation in both legs, the right arm and thoracic paraspinal muscles.

Over the next four years she progressed slowly, but continued to work at a desk job, wore bilateral ankle braces and occasionally used a walker. She denied dysarthria, dysphagia or shortness of breath. Examination showed an FVC 84% of predicted. She had 4+/5 proximal and intermediate arm strength, 2–3/5 hand muscle strength and 3–4/5 proximal and intermediate leg strength, all worse on the right. There was trace ankle and no toe movement. Tone was normal. DTRs were present and a Babinski response was noted on the right. Gait showed bilateral foot drop.

III 13 noted diffuse left arm and leg weakness resulting in several falls at age 67 years. Weakness progressed minimally over the next three years, but she stumbled frequently and held on to her husband while walking. Two years after symptom onset she and her husband noted dysarthria, dysphagia and progressive cognitive difficulties with inability to perform household tasks and bills, poor judgment, and trouble with short-term recall. MRI of the brain, cervical spine and lumbar spine were normal. Neurologic examination showed mild bifacial weakness and spastic dysarthria. FVC was 96% of predicted. Strength was 4/5 in the left arm and leg with normal strength elsewhere. Mild spasticity and slow movements were noted on the left more than right. There were choreiform movements of both arms. DTRs were brisk including right ankle clonus. Her gait was spastic. EMG carried out twice on several muscles in bilateral arms and legs was normal.

She progressed slowly over the next two years, with more frequent falls due to a spastic gait and, according to her husband, poor decision making. She denied shortness of breath. Examination showed palmomental and grasp reflexes. She had spastic speech and her FVC was 77% of predicted. There was 4–/5 strength in the left arm and leg with spasticity, but no atrophy. Strength on the right was 4+/5 with normal tone. DTRs were brisk. She had dystonic and choreiform movements of her face, arms and legs and a spastic gait. Detailed neurobehavioral testing showed global deficits involving verbal fluency, executive abilities, and visual spatial skills with sparing of episodic memory consistent with mild frontotemporal dementia.

Discussion

There are few reports of clinical manifestations from pedigrees with the I113T SOD1 mutation (3,6,7), but detailed descriptions in multiple affected patients are lacking. Our description of this large family highlights the extreme clinical intrafamilial variability caused by this mutation. The variable and late age of onset, and long survival time in this family are similar to earlier descriptions. In the eight symptomatic patients, age of onset varied from 37 to 67 years. The mean age of 53 years is similar to previously reported averages of 50–60 years, much later than in other SOD1 mutations (2,8). Disease duration ranged from two to 10 years, also similar to the 3.5–20 years previously reported (2,8). One likely explanation for this long disease duration is that patients may have only fasciculations for many years, with minimal weakness. Two of our patients had fasciculations or cramps as the only symptoms for five and 10 years, both with only mild findings on examination. While about 5% of ALS patients may present solely with fasciculations (9), a prolonged course with fasciculations and minimal weakness has not been described in families with the I113T mutation.

Incomplete penetrance, which may partly explain the high rate of this mutation in sporadic patients, has not been reported to the extreme as in the family reported here. Of the 15 patients with the mutation, five had no symptoms and four had mild complaints but no weakness. Six of these patients had normal examinations, one was not examined but had no complaints, and two had only minimally abnormal examinations. The 86-year-old patient complained of difficulty walking with occasional falls due to pain and had a normal neurologic examination. The penetrance of 50% at age 60 years, and 88% at age 80 years differs from a previous report in which no patient with an I113T mutation lived past age 78 years, with a penetrance of 95% by age 78 years (7). While reduced penetrance is not exclusive to the I113T mutation (10), it complicates diagnosis and genetic counseling, which should only be undertaken after detailed genealogical evaluation (11).

The most unique aspect of this family is the extreme variability in clinical manifestations, most obvious in the descendants of II 3. III 16 had no symptoms, while his daughter had symptoms of mild ALS. III 15 had prominent distal numbness and weakness as her presenting complaint. Sensory symptoms have been reported in FALS patients (11), but not in patients with the I113T mutation. The most unique patient, III 13, had primarily UMN features (two EMGs were normal), prominent frontotemporal dementia and chorea/dystonia on examination, while her daughter had fairly typical signs and symptoms of ALS. No patient with predominant UMN features has been reported in FALS patients (5), and while frontotemporal dementia is present in 5% of SALS (1), it is rarely reported in FALS (14), with no good description in a patient with the I113T mutation. There are rare reports of patients with extrapyramidal features (12,13) including chorea, retropulsion, rigidity and bradykinesia, and neuropathological examination in FALS patients can include degeneration in areas outside the motor system. A family with the I113T mutation had neurofibrillary tangles in the globus pallidus, substantia nigra and locus coeruleus, although no patient had extrapyramidal signs or symptoms (6).

Clinical heterogeneity has been described in many autosomal dominantly inherited diseases including in several SOD1 mutations (3,6,14), although the reason for this variability is unknown in patients with SOD1 mutations. The site of SOD1 mutation is unlikely to be related since more than 140 mutations affecting nearly 50% of all amino acids have been found uniformly throughout the gene. A more likely explanation is that more than one genetic mutation may be needed to cause complete manifestation, or that a second mutation or polymorphism may modify the original phenotype. Association studies have found several genes with a possible modifying role in FALS (15), and we are currently investigating for genetic modifiers in this family. Ultimately, the reason for clinical heterogeneity in patients with the I113T SOD1 mutation may shed light onto the underlying pathogenetic mechanisms responsible for both FALS and SALS.

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